REMARKS

The subject matter claimed relates in part to methods for predicting the likelihood of a subsequent cerebral vasospasm in patients presenting with subarachnoid hemorrhage.

Claims 1, 5, 8, 11, 14-16, and 18-26 are pending herein. Applicants request reconsideration of the claimed invention in view of the following remarks.

1. 35 U.S.C. §112, Second Paragraph (definiteness)

Applicants respectfully traverse the rejection of claims 1, 5, 8, 11, 14-16, and 18-26 as allegedly failing to satisfy the definiteness standard of 35 U.S.C. §112, second paragraph.

The Examiner asserts that the claims are allegedly indefinite for incorporating "a broad range or limitation together with a narrow range or limitation." The clause of claim 1 to which the Examiner objects reads as follows:

> ... determining the presence or amount of a plurality of subject-derived markers in a sample obtained from said subject, wherein said plurality of markers are independently selected from the group consisting of specific markers of neural tissue injury, markers related to blood pressure regulation, markers related to inflammation, and markers related to apoptosis,
>
> provided that one or more of said subject-derived markers are selected from the group consisting of neural cell adhesion molecule (NCAM), vascular endothelial growth factor (VEGF), B-type natriuretic peptide (BNP), NT-pro BNP, pro-BNP, matrix metalloprotease-9 (MMP-9), caspase-3, and von Willebrand factor (vWF), or markers related thereto ...

Applicants respectfully submit that this language is absolutely clear on its face. The claim requires determining the presence or amount of a plurality of markers selected from among specific markers of neural tissue injury, markers related to blood pressure regulation, markers related to inflammation, and markers related to apoptosis, with the proviso that at least one of that plurality of markers must be selected from the group consisting of neural cell adhesion molecule (NCAM), vascular endothelial growth factor (VEGF), B-type natriuretic peptide (BNP), NT-pro BNP, pro-BNP, matrix metalloprotease-9 (MMP-9), caspase-3, and von Willebrand factor (vWF), or markers related thereto.

MPEP § 2173.05 and EX PARTE YULIN WU, 10 U.S.P.Q.2d 2031 (Bd.Pat.App & Interf. 1988), each cited by the Examiner, caution that an examiner must analyze claims on a case by case basis with regard to definiteness. The Examiner simply asserts that a blanket rule exists that claims incorporating "a broad range or limitation together with a narrow range or limitation" are considered *per se* indefinite. *See, e.g.*, Office Action, page 2 ("[a] broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite) (emphasis added). It is not clear on what legal precedence, or what logical reasoning, this assertion is based. For this reason alone, the rejection fails to establish that the claims are vague or indefinite.

Furthermore, none of the citations discussed by the Examiner supports a conclusion that claim 1 as presently written is indefinite. For example, MPEP § 2173.05 concerns the use of narrow and broad *numerical* ranges. Claim 1 does not contain such ranges; in fact, no numerical ranges are present in the claim. Similarly, the Board of Patent Appeals cases discussed by the Examiner relate to the use of phrases like "for example" and "such as" in claims. Claim 1 does not contain such language. And there can be no confusion from the language in claim 1 that the proviso language quoted above is *not* "merely exemplary of the remainder of the claim, and therefore not required", as alleged by the Examiner.

When determining definiteness, the proper standard to be applied is "whether one skilled in the art would understand the bounds of the claim when read in the light of the specification." *Credle v. Bond*, 30 USPQ2d 1911, 1919 (Fed. Cir. 1994). Definiteness is not analyzed in a vacuum, but in light of the content of the specification, and with the knowledge available to the skilled artisan. When viewed in this light, a claim must reach the level of being "insolubly ambiguous" in order to be indefinite. See, e.g., *Scripps Research Institute v. Nemerson and Konigsberg*, 78 U.S.P.Q.2d 1019, 1030 (Bd. Pat. App & Interf. 2005). When measured by the proper standard, the present claims satisfy 35 U.S.C. §112, second paragraph.

Applicants respectfully submit that the claims meet the definiteness standard of 35 U.S.C. §112, second paragraph, and request that the rejection be reconsidered and withdrawn.

2. 35 U.S.C. §102

Applicants respectfully traverse the rejection of claims 1, 14, 16, and 19-21 as allegedly being anticipated by Sviri *et al., Stroke* 31: 118-122, 200. Applicants submit that no *prima facie* case of anticipation has been established.

The present claims refer to a method characterizing a risk of future cerebral vasospasm in a subject suffering from a subarrachnoid hemorrhage. In contrast, Sviri *et al.* only looks at BNP concentrations as they relate to a previously suffered cerebral vasospasm. Sviri *et al.* looks at 19 patients who have had a subarrachnoid hemorrhage, and they compare BNP levels measured in four periods: 1-3 days after subarrachnoid hemorrhage, 4-6 days after, 7-9 days after, and 10-12 days after. The existence of a current cerebral vasospasm is identified in 13 of the patients through the measurement of flow velocities by transcranial Doppler recordings. Sviri *et al.*, page 119, sections entitled "Transcranial Doppler Recording Technique" and "Vasospasm."

The Examiner states that "[t]he purpose of [Sviri *et al.*] was to investigate the relationship between BNP plasma concentrations and cerebral vasospasm after anuerysmal SAH." Office Action, page 3. However, the Examiner's assertion that this "purpose" of Sviri *et al.* is equivalent to the claimed invention is incorrect. It is not.

The authors note that in patients identified as already having suffered cerebral vasospasm, BNP increases in the third (7-9 day) period compared to the first (1-3 day) period. Sviri *et al.*, page 120. The authors also state, however, that in this small population of patients, BNP does not correlate with flow velocities or with neurological condition on admission of the patient. Sviri *et al.*, page 122, left column. Moreover, the authors suggest that BNP does not rise until a vasospasm has already occurred. Sviri *et al.*, page 121, right column ("BNP levels showed a continuous trend of elevation only in patients with symptomatic vasospasm). Because of this, the authors consider it plausible that "the vasospasm itself may be responsible for hypothalamic ischemia.... This hypothalamic ischemic insult may in turn induce BNP secretion." Sviri *et al.*, page 122, left column. If Sviri *et al.* believes that the vasospasm might be causing the increase in

BNP, how could one conclude from Sviri *et al.* that BNP might predict a future vasospasm? The clear answer is that one could not draw that conclusion.

Thus, in sharp contrast to the Examiner's interpretation of Sviri *et al.*, it is clear that the authors of that publication did not believe that they were providing a method for characterizing a risk of future cerebral vasospasm in a subject suffering from a subarrachnoid hemorrhage. And when properly considered, it is plain that Sviri *et al.* does not teach, or even fairly suggest, that BNP can be used to characterize a risk of future cerebral vasospasm in a subject suffering from a subarrachnoid hemorrhage. Therefore, based on the preceding alone, Sviri *et al* cannot be held to anticipate the rejected claims.

In addition, the present claims require the determining the presence or amount of a plurality of subject-derived markers in a sample obtained from said subject, and correlating the presence or amount of that plurality of markers to the subject's risk of future cerebral vasospasm. The Examiner does not assert that Sviri *et al.* meets this limitation of the claims.

The Examiner does, however assert that "the measurement of BNP necessarily measures NT-proBNP and pro-BNP because they all contain the same BNP sequence." Office Action, page 4. This is incorrect. Pro-BNP is a 180-residue precursor to the BNP and NT-proBNP molecules. Pro-BNP is cleaved between residues 76 and 77 to provide BNP (residues 77-108) and NT-proBNP (residues 1-76). An assay which is used by the artisan to determine, for example, a BNP concentration is not the same as an assay used to determine an NT-proBNP concentration. Likewise, an assay that detects neither BNP nor NT-proBNP can be used to determine a pro-BNP concentration.

Because no *prima facie* case of anticipation has been established, Applicants respectfully request that the rejection be reconsidered and withdrawn.

3. 35 U.S.C. §103

Applicants respectfully traverse the rejection of claims 22-24 as allegedly being unpatentable under 35 U.S.C. § 103(a) over Sviri *et al.*, discussed above, in view of Jackowski, WO00/52476. Applicants submit that no *prima facie* case of obviousness has been established.

As discussed above, the Examiner's characterization of Sviri *et al.* is incorrect. In this rejection, as in the anticipation rejection discussed above, Sviri *et al.* is relied upon for allegedly teaching the use of BNP to assess a risk of future cerebral vasospasm in a subject suffering from a subarrachnoid hemorrhage. As discussed in detail above, even the authors of that publication did not believe that they were providing such a method.

Moreover, even if the Examiner's characterization of the secondary Jackowski publication is correct, that characterization is also irrelevant to the claimed invention. The Examiner relies on this secondary reference for allegedly disclosing "methods for assessing stroke", "markers [that] can distinguish between ischemic and hemorrhagic events", "that stroke is routinely diagnosed with a cat scans", "determination of a plurality of derived markers which are correlated to a subarachnoid hemorrhage", *etc.* Office Action, pages 5 and 6. But, like Sviri *et al.*, all of the disclosure in the secondary Jackowski publication has to do with identifying the presence of a current event. Jackowski does not even hint that any biomarker tests could be used to assign a risk of future cerebral vasospasm in a subject suffering from a subarrachnoid hemorrhage, which is the subject of the present claims. Indeed, Jackowski never mentions cerebral vasospasm at all. Jackowski appears to be cited solely because it has something generally to do with stroke diagnosis, which is then vaguely related by the Examiner to the subject matter of the present claims.

The Examiner's assertions that it would have been obvious to combine these two publications to "distinguish and/or differentiate between ischemic and hemorrhagic events" or "to assess and monitor brain damage and aid in patient treatment" (Office Action, page 6) do not relate in any way to the claimed invention. Even if combined as suggested by the Examiner, the

resulting combination could at best identify the current disease state of the subject under study. And such a combination would not perform the claimed methods, as no correlation of assay results to risk of a future cerebral vasospasm would result from practicing that combination.

Because no *prima facie* case of obviousness has been established, Applicants respectfully request that the rejection be reconsidered and withdrawn.

4. 35 U.S.C. §103

Applicants respectfully traverse the rejection of claims 5 and 15 as allegedly being unpatentable under 35 U.S.C. § 103(a) over Sviri *et al.*, discussed above, in view of Ronn *et al.*, WO00/18801. Applicants submit that no *prima facie* case of obviousness has been established.

As discussed above, the Examiner's characterization of Sviri *et al.* is incorrect. In this rejection, as in the anticipation rejection discussed above, Sviri *et al.* is relied upon for allegedly teaching the use of BNP to assess a risk of future cerebral vasospasm in a subject suffering from a subarrachnoid hemorrhage. As discussed in detail above, even the authors of that publication did not believe that they were providing such a method.

Moreover, even if the Examiner's characterization of the secondary Ronn *et al.* publication is correct, that characterization is also irrelevant to the claimed invention. The Examiner relies on this secondary reference for allegedly disclosing the use of NCAM as a marker of "several disorders including stroke" Office Action, page 7. But, like Sviri *et al.*, all of the disclosure in the secondary Ronn *et al.* publication has to do with identifying the presence of a current event. Ronn *et al.*, like the secondary Jackowski publication discussed above, is completely silent on the subject of assigning a risk of future cerebral vasospasm in a subject suffering from a subarrachnoid hemorrhage, which is the subject of the present claims. And Ronn *et al.*, like the secondary Jackowski publication discussed above, appears to be cited solely because it has something generally to do with stroke diagnosis, and is then vaguely related by the Examiner to the subject matter of the present claims.

The Examiner's assertion that it would have been obvious to combine these two publications to "use NCAM as a marker for stroke" (Office Action, page 7) does not relate in any way to the claimed invention. Even if combined as suggested by the Examiner, the resulting combination could at best identify the current disease state of the subject under study. And such a combination would not perform the claimed methods, as no correlation of assay results to risk of a future cerebral vasospasm would result from practicing that combination.

Because no *prima facie* case of obviousness has been established, Applicants respectfully request that the rejection be reconsidered and withdrawn.

5. 35 U.S.C. §103

Applicants respectfully traverse the rejection of claims 8 and 15 as allegedly being unpatentable under 35 U.S.C. § 103(a) over Sviri *et al.*, discussed above, in view of Yakolev *et al.*, *J. Neurosci.* 17: 7415-24, 1997. Applicants submit that no *prima facie* case of obviousness has been established.

As discussed above, the Examiner's characterization of Sviri *et al.* is incorrect. In this rejection, as in the anticipation rejection discussed above, Sviri *et al.* is relied upon for allegedly teaching the use of BNP to assess a risk of future cerebral vasospasm in a subject suffering from a subarrachnoid hemorrhage. As discussed in detail above, even the authors of that publication did not believe that they were providing such a method.

Moreover, even if the Examiner's characterization of the secondary Yakolev *et al.* publication is correct, that characterization is also irrelevant to the claimed invention. The Examiner relies on this secondary reference for allegedly disclosing that "caspase-3 levels were elevated in brain injury" Office Action, page 8. But, like Sviri *et al.*, all of the disclosure in the secondary Yakolev *et al.* publication has to do with identifying the presence of a current event. Yakolev *et al.*, like the other secondary publications cited by the Examiner in the Office Action, is completely silent on the subject of assigning a risk of future cerebral vasospasm in a subject suffering from a subarrachnoid hemorrhage, which is the subject of the present claims. Like the

other secondary publications cited by the Examiner in the Office Action, Yakolev *et al.* appears to be cited solely because it has something generally to do with stroke diagnosis.

The Examiner's assertion that it would have been obvious to combine these two publications to "because Yakolev et al. taught that caspase-3 levels were elevated in brain injury and the inhibition of caspase-3 markedly attenuates [traumatic brain injury] in vivo and improved neurological recovery" (Office Action, page 8) does not relate in any way to the claimed invention. In particular, Applicants note that traumatic brain injury is not even tenuously related by the Examiner to the claimed subject of cerebral vasospasm following a subarrachnoid hemorrhage.

Even if combined as suggested by the Examiner, the resulting combination could at best identify the current disease state of the subject under study. And such a combination would not perform the claimed methods, as no correlation of assay results to risk of a future cerebral vasospasm would result from practicing that combination.

Because no *prima facie* case of obviousness has been established, Applicants respectfully request that the rejection be reconsidered and withdrawn.

6. 35 U.S.C. §103

Applicants respectfully traverse the rejection of claims 11 and 15 as allegedly being unpatentable under 35 U.S.C. § 103(a) over Sviri *et al.*, discussed above, in view of Greenberg, *Drug News and Perspectives* 11: 265-70, 1998. Applicants submit that no *prima facie* case of obviousness has been established.

As discussed above, the Examiner's characterization of Sviri *et al.* is incorrect. In this rejection, as in the anticipation rejection discussed above, Sviri *et al.* is relied upon for allegedly teaching the use of BNP to assess a risk of future cerebral vasospasm in a subject suffering from a subarrachnoid hemorrhage. As discussed in detail above, even the authors of that publication did not believe that they were providing such a method.

Moreover, even if the Examiner's characterization of the secondary Greenberg publication is correct, that characterization is also irrelevant to the claimed invention. The Examiner relies on this secondary reference for allegedly disclosing that "stroke results from focal cerebral ischemia due to the occlusion of cerebral blood vessels (angiogenesis).... Greenberg taught that VEGF is a key mediator of angiogenesis and cerebral ischemia." Office Action, page 9. However, Greenberg, similar to the other secondary publications cited by the Examiner, is completely silent on the subject of assigning a risk of future cerebral vasospasm in a subject suffering from a subarrachnoid hemorrhage, which is the subject of the present claims.

Moreover, Applicants note that a "stroke result[ing] from focal cerebral ischemia" is not related to the subject of cerebral vasospasm following a subarrachnoid hemorrhage. A subarrachnoid hemorrhage is not a type of focal ischemic event; it is a hemorrhagic event. Like the other secondary publications cited by the Examiner in the Office Action, Greenberg appears to be cited solely because it is merely generally related with stroke diagnosis, and is then vaguely related by the Examiner to the subject matter of the present claims.

Even if combined as suggested by the Examiner, the resulting combination could at best identify the current disease state of the subject under study. And such a combination would not perform the claimed methods, as no correlation of assay results to risk of a future cerebral vasospasm would result from practicing that combination.

Because no *prima facie* case of obviousness has been established, Applicants respectfully request that the rejection be reconsidered and withdrawn.

7. 35 U.S.C. §103

Applicants respectfully traverse the rejection of claim 18 as allegedly being unpatentable under 35 U.S.C. § 103(a) over Sviri *et al.*, discussed above, in view of each of Greenberg, Ronn *et al.*, and Yakolev *et al.*, also discussed above. Applicants submit that no *prima facie* case of obviousness has been established.

As discussed above, the Examiner's characterization of Sviri *et al.* is incorrect. In this rejection, as in the anticipation rejection discussed above, Sviri *et al.* is relied upon for allegedly teaching the use of BNP to assess a risk of future cerebral vasospasm in a subject suffering from a subarrachnoid hemorrhage. As discussed in detail above, even the authors of that publication did not believe that they were providing such a method.

The attempt by the Examiner to identify various secondary publications that discuss some facet of stroke diagnosis, and then assert that such publications are somehow relevant to the subject matter of the present claims, is perhaps most plainly evident in this rejection. Each of the three secondary publications is said by the Examiner to "teach the use of the respective markers in stroke and/or cerebral injuries." Office Action, page 10. Whether true or not, what is absolutely true is that none of the secondary publications even mention assessing a risk of future cerebral vasospasm in a subject suffering from a subarrachnoid hemorrhage, or indeed even suggest that such a method is possible.

Applicants note that the present claims do not relate to the general "use of markers in stroke and/or cerebral injuries." Rather, the present claims are very specific in reciting that the claimed methods are for assigning a risk of future cerebral vasospasm in a subject suffering from a subarrachnoid hemorrhage. Rejections on obviousness grounds cannot be sustained by vague statements that are not directed to the language of the claims; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion that the claims as written are obvious. *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1741 (2007) (quoting *In re Kahn*, 441 F.3d 977, 988, 78 U.S.P.Q.2d 1329, 1336 (Fed. Cir. 2006)).

Even if combined as suggested by the Examiner, the resulting combination could at best identify the current disease state of the subject under study. And such a combination would not perform the claimed methods, as no correlation of assay results to risk of a future cerebral vasospasm would result from practicing that combination.

Because no *prima facie* case of obviousness has been established, Applicants respectfully

request that the rejection be reconsidered and withdrawn.

8. 35 U.S.C. §103

Applicants respectfully traverse the rejection of claim 25 as allegedly being unpatentable under 35 U.S.C. § 103(a) over Sviri *et al.*, discussed above, in view of Montaner *et al.*, *Stroke* 32: 1759-66, 2001. Applicants submit that no *prima facie* case of obviousness has been established.

As discussed above, the Examiner's characterization of Sviri *et al.* is incorrect. In this rejection, as in the anticipation rejection discussed above, Sviri *et al.* is relied upon for allegedly teaching the use of BNP to assess a risk of future cerebral vasospasm in a subject suffering from a subarrachnoid hemorrhage. As discussed in detail above, even the authors of that publication did not believe that they were providing such a method.

Moreover, even if the Examiner's characterization of the secondary Montaner *et al.* publication is correct, that characterization is also irrelevant to the claimed invention. The Examiner relies on this secondary reference for allegedly disclosing "the overexpression on MMP-9 levels in stroke" Office Action, page 11. But, like Sviri *et al.*, all of the disclosure in the secondary Montaner *et al.* publication has to do with identifying the presence of a current event. Montaner *et al.*, like the other secondary publications cited by the Examiner, is completely silent on the subject of assigning a risk of future cerebral vasospasm in a subject suffering from a subarrachnoid hemorrhage, which is the subject of the present claims.

Applicants note that Montaner *et al.* is directed to focal ischemic stroke. A stroke resulting from focal cerebral ischemia is not related to the subject of cerebral vasospasm following a subarrachnoid hemorrhage. As noted above, a subarrachnoid hemorrhage is not a type of focal ischemic event; it is a hemorrhagic event. Like the other secondary publications cited by the Examiner in the Office Action, Montaner *et al.* appears to be cited solely because it has something generally to do with stroke diagnosis.

Even if combined as suggested by the Examiner, the resulting combination could at best identify the current disease state of the subject under study. And such a combination would not perform the claimed methods, as no correlation of assay results to risk of a future cerebral vasospasm would result from practicing that combination.

Because no *prima facie* case of obviousness has been established, Applicants respectfully request that the rejection be reconsidered and withdrawn.

9. 35 U.S.C. §103

Applicants respectfully traverse the rejection of claim 25 as allegedly being unpatentable under 35 U.S.C. § 103(a) over Sviri *et al.*, discussed above, in view of Liu *et al.*, *Thrombosis Res.* 72: 353-358, 1993. Applicants submit that no *prima facie* case of obviousness has been established.

As discussed above, the Examiner's characterization of Sviri *et al.* is incorrect. In this rejection, as in the anticipation rejection discussed above, Sviri *et al.* is relied upon for allegedly teaching the use of BNP to assess a risk of future cerebral vasospasm in a subject suffering from a subarrachnoid hemorrhage. As discussed in detail above, even the authors of that publication did not believe that they were providing such a method.

Moreover, even if the Examiner's characterization of the secondary Liu *et al.* publication is correct, that characterization is also irrelevant to the claimed invention. In Liu *et al.*, the Examiner has referenced a publication that is related to the subject of hemorrhagic stroke. But the Examiner relies on this secondary reference solely for allegedly disclosing that "vWF levels are increased in both thrombotic and hemorrhagic stroke, and vWF and antithrombin III levels differ between thrombotic and hemorrhagic stroke in patients with high incidence of atherosclerosis." Office Action, page 12. The relevance of this reference to the subject matter of the present claims is not addressed.

In this case, no attempt is made to relate the teachings of the secondary Liu *et al.* publication to the subject matter of the present claims. Similar to the other secondary publications cited by the Examiner, Liu *et al.* does not disclose assessing a risk of future cerebral vasospasm in a subject suffering from a subarrachnoid hemorrhage, or indeed even suggest that such a method is possible. Furthermore, as with the other secondary publications cited by the Examiner in the Office Action, Montaner *et al.* appears to be cited solely because it has something generally to do with stroke diagnosis.

Even if combined as suggested by the Examiner, the resulting combination could at best identify the current disease state of the subject under study. Therefore, such a combination would not teach or suggest the claimed methods, because no correlation of assay results to risk of a future cerebral vasospasm would result.

Because no *prima facie* case of obviousness has been established, Applicants respectfully request that the rejection be reconsidered and withdrawn.

CONCLUSION

Applicants respectfully submit that the pending claims are in condition for allowance. An early notice to that effect is earnestly solicited. Should any matters remain outstanding, the Examiner is encouraged to contact the undersigned at the address and telephone number listed below so that they may be resolved without the need for additional action and response thereto.

Respectfully submitted,

Date April 4, 2008

By _____

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